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Version: Published Version

Article:

Thompson, Charis (2019) How should “CRISPRed” babies be monitored over their life course to promote health equity? *AMA Journal of Ethics*, 21 (12). E1036-1041. ISSN 2376-6980

<https://doi.org/10.1001/amajethics.2019.1036>.

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CASE AND COMMENTARY

How Should “CRISPRed” Babies Be Monitored Over Their Life Course to Promote Health Equity?

Charis Thompson, PhD

Abstract

Gene-edited babies who might be born in the future should be monitored over the course of their life. These patients’ physical, mental, and social health monitoring should be coordinated by clinicians in ways that anonymize patients’ data for privacy protection but also allow for national and international aggregate evaluations. Transnational monitoring efforts should focus on safety and efficacy, social and disability justice, what constitutes the standard of care, and how best to promote both access to care and social and genomic research and innovation. In addition, effective and binding mechanisms for stopping or limiting uses of gene editing technology should be developed.

Case

Dr L and her team are germline editing researchers who are about to begin work with Dr M at her university hospital fertility clinic on a germline genome editing pilot protocol approved after extensive public comment and review by ethical, safety, disability and social justice, and regulatory bodies. Four couples in which both partners are carriers for well-studied severe monogenic conditions have given their consent to be involved in the clinical trial.

Later in the week, Dr L, Dr M, and the couples will be meeting with Dr C and Dr D, who have been designated as the long-term monitoring physicians for physical and mental health, respectively, for any children born from this trial. They will also be meeting with Dr Q, a bioethics specialist, who will be monitoring the social aspects of follow-up care. The purpose of these meetings is to debrief with clinical teams about what kind of follow-up monitoring, care, and feedback are appropriate. What should they cover in these meetings? How should babies who underwent germline genome editing be monitored over the course of their life?

Commentary

The world’s first known “CRISPRed” babies, Chinese twin girls, were born in October 2018 after researcher He Jiankui used clustered regularly interspaced short palindromic repeat (CRISPR) technology to disable a gene called CCR5 in their genomes so as to

render the babies immune to HIV.¹ Their father is HIV positive; their mother, the primary clinical patient-subject from whom the eggs were extracted and who gestated her twin pregnancy after the genome-edited embryos were transferred to her uterus, is HIV negative.¹ This case brought home to the world the reality of germline genome edited, or CRISPRed, babies. Not only have the girls' genome been altered; if the girls later reproduce using their own eggs, their resultant children will inherit the genetic modification, which in turn is heritable down subsequent generations. Neither girl had—nor will any of their genetic descendants have—the option of consenting to this modification. To many in China and the West, it was legally questionable, ethically problematic, scientifically premature, and clinically unnecessary to take CRISPR clinical at the time and for the condition in question.¹ The absence of guidelines and mechanisms for follow-up care and monitoring of the babies, together with a lack of clear pathways by which feedback from such monitoring might be used to improve or halt CRISPR as appropriate, highlights the sense of prematurity. This is the right moment to plan ahead for comprehensive monitoring and care should there be any future CRISPRed births.

Types of Monitoring

Physical. Monitoring of CRISPRed children needs to be guided first and foremost by the children's well-being. This purpose should never be displaced by scientific goals. Dr L (the genome editing researcher), Dr M (the assisted reproductive technology clinician), and the couples should draw up a plan with Dr C (the primary care and coordinating physician) for monitoring and, when necessary, mitigating physical effects of the modification. It is likely that karyotyping and genome sequencing would be recommended. This can be done prenatally or postnatally using biopsy or phlebotomy methods commonly available in resource-rich countries during routine prenatal or postnatal care. This information would allow Dr L and Dr M to check for genetic mosaicism—the incomplete penetration of CRISPR-mediated DNA edits—and to screen for unintended off-target effects. Knowing the efficacy and precision of the intervention might leave health-related questions unanswered at first because clinical consequences of an intended edit and of off-target or incomplete effects will be unknown. The clinical justification for collecting this data, however, is to begin to build an evidence base for future understanding and care. To reach this goal, there should be a centralized mandatory digital reporting facility with international oversight that would collect anonymized, privacy-protected data on every CRISPRed child. The data in this repository should be tied to and inform ongoing medical care and scientific and social policy. The World Medical Association, together with the World Health Organization and its statistics repository, the Global Health Observatory,² would be an ideal locus for this international data collation. The United Nations Convention on the Rights of Persons with Disabilities,³ the Oviedo Convention,⁴ and reproductive data collection efforts such as the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System are examples of important potential national and international regulatory and data collection partners.

CRISPRed babies and children should be monitored throughout their lives in a routine manner, with additional scrutiny for residual effects of the original disease or condition for which the technique was employed in the first place and for any physical effects that might be linked to the intended edit or to off-target effects. The baseline against which their health and well-being should be evaluated should be the health of those receiving standard of care for the condition but whose genomes were not edited. Although in practice standard of care varies according to local biomedical infrastructure and health care access, if CRISPR applications are translated to the clinic, every effort should be made to adopt the highest standard of care found anywhere in the world for the condition in question. To do so is not just a matter of [health equity](#). Because germline modifications are heritable, they have planetary implications and should not be given a green light in [resource-poor settings](#) simply because it is easier to prove relative efficacy and safety against a lower standard of care.

Following childhood, in which the health status and milestones of CRISPRed children are measured against those of children receiving standard of care for the condition, adolescence would be a period for special physical monitoring and care, particularly regarding puberty and the morphology and changes in the DNA of germ cells, which could profoundly influence descendants' reproductive futures. Continuity of prenatal and postnatal care and from childhood through adolescence and beyond should be prioritized. It is important that women who provide eggs or gestation for CRISPRed babies also have their physical health evaluated regularly and that their anonymized privacy-protected data be linked to descendants' data.

Mental health. In a similar manner, Dr L, Dr M, and the couples should draw up a plan with Dr D (the mental health practitioner and coordinator) to monitor childhood milestones and be ready for early intervention if signs of mental health risks emerge in childhood, adolescence, or adulthood. Particular attention should be paid to how the child's understanding of his or her origins might affect the child's sense of autonomy. As a result of disclosure, the child might have difficulty trusting health professionals, which might influence how the child interacts in future with the health care community. The child might experience anxiety related to having been edited or having an unknown biological future. The child's relations to others living with the condition for which the child has been edited also could be complicated. And the impact of widespread public antigenome editing sentiment might affect the child's well-being.

Mental health services would need to be available in case the child came to resent having been edited or being targeted by opponents of germline editing. Mindful efforts should also be made by the whole care team to pre-emptively involve the child or adolescent in directing his or her future and the future of CRISPR, including consideration of options to have the edit clinically reversed in some of their own cells (via somatic genome editing) or their offspring's cells (via germline genome editing). Dr D should also monitor family-

level mental health and arrange treatment, as appropriate, given that a family is likely to be a significant unit of well-being for the child.

Social issues. When Dr L, Dr M, and the couples meet with Dr Q (the bioethicist and social coordinator), they should discuss which social issues need monitoring and how to begin to do that. Crucially, Dr Q will need to liaise with clinicians, insurance companies, and policymakers to ensure access to and affordability of treatment and comprehensive long-term monitoring of and health care for CRISPRed babies, regardless of ability to pay. Other core considerations include ethical questions about monitoring itself, such as ensuring consent to participate in monitoring and [privacy of data](#) collected during monitoring. Questions about monitoring also compass science and industry relations—for example, whether any children's data were used for research and innovation. Might the family, and later the child, consent to allow use of the child's anonymized data to improve the CRISPR process itself or the care of others with the condition from which they might otherwise have suffered? Should they or causes with which they are associated benefit from any profit sharing or other returns from a profitable biomedical innovation? Plans will also need to be in place to develop international regulatory standards. Without shared international standards and regulations, medical tourism by and for the wealthy, exploitation of lower-resourced egg donors or surrogates or clinical trial participants across borders, and nonevidence-based treatment advertising are all likely to develop and to exacerbate inequalities of nation, class, and race.^{5,6}

The families and Dr Q should also discuss how to liaise with health and disability justice activists so that information can be passed among all parties about what it means to experience removal from the genome of a kind of embodiment shared with others. Given that CRISPR risks increasing ableism and diverting resources from the specific condition for which it was used, monitoring in this area is essential to protect the [reproductive futures and rights](#) of those living with the condition and those living with disabilities and chronic disease in general. Mechanisms such as regular voluntary meetings among CRISPRed persons and their carers and those living with disability should be put in place to increase solidarity and decrease stigma and ableism. Together, stakeholders could develop standards for unacceptable exacerbation of inequalities, violations of which could trigger responses up to and including a return to a moratorium on germline genome editing should that be deemed the most socially acceptable path. It would be vital to monitor national and international opinion about conditions for which germline genome editing is deemed safe, efficacious, and socially and ethically acceptable and to put in place mechanisms and instruments to halt temporarily or permanently modifications that fail to meet the highest ethical, social, or scientific and clinical standards or that turn out to have significant negative effects on particular groups or on society as a whole.

Finally, Dr L (the genome editing researcher), Dr M (the reproductive technology clinician) and the couples should discuss with Dr C (the primary care physician and physical health coordinator), Dr D (the mental health practitioner and coordinator), and Dr Q (the bioethicist and social coordinator) how to be kept informed about and to participate voluntarily in efforts to coordinate collection of data at national and international levels on ethical, social, and scientific issues and for purposes of [research and innovation](#). (The National Institutes of Health's All of Us Research Program is an important model for this approach.⁷) It will be clinically important for all CRISPRed children to leverage as much robust medical information as possible in making health decisions. Monitoring should always be accompanied by mandates to provide care and to address patterns emerging from the data. The more that flexible but uniform policies can be developed that respect the human rights and dignity of CRISPRed children as well as justice for all others affected by CRISPR, the easier it will be to implement scientific and ethical safeguards for human germline genome editing.

Conclusion

In conclusion, with the help of physicians and other coordinators—and for purposes of setting scientific, clinical, and social policy on genome editing—national and international bodies should at minimum collect data on the following for babies who underwent genome editing as embryos: physical and mental well-being over the life course; efficacy of the editing process relative to standard of care; unintended effects; economic aspects of innovation and access to affordable health care; social effects upon the children themselves and their families; and effects upon individuals living with the condition and on the wider society as selecting against human variation becomes more common.

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Editor's Note

The case to which this commentary is a response was developed by the editorial staff.

Citation

AMA J Ethics. 2019;21(12):E1036-1041.

DOI

10.1001/amajethics.2019.1036.

Conflict of Interest Disclosure

The author(s) had no conflicts of interest to disclose.

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ISSN 2376-6980